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HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

| EXAMINER | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/537,176 | SOMMERMEYER, KLAUS | |
| | Examiner | Art Unit | |
| | SCARLETT GOON | 1623 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *35-69* is/are pending in the application.

4a) Of the above claim(s) *54-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-53 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12 August 2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

This Office Action is in response to Applicant's Remarks filed on 12 August 2010.

The Declaration of Dr. Klaus Sommermeyer (inventor), submitted by Applicant on 12 August 2010 under 37 CFR § 1.132, is acknowledged and will be further discussed below.

Claims 35-69 are pending in the instant application.

Claims 54-68 were previously withdrawn from further consideration in the Office Action dated 8 December 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or nonelected species, there being no allowable generic or linking claim.

Claims 35-53 and 69 are examined on its merits herein.

***Priority***

This application is a National Stage entry of PCT/EP03/13622 filed on 3 December 2003 and claims priority to Germany foreign application 10256558.9 filed on 4 December 2002. A certified copy of the foreign priority document in German has been received. An English translation of the foreign priority document, and a statement verifying the accuracy of the English translation, was received at the Office on 12 August 2010.

***Information Disclosure Statement***

The information disclosure statement (IDS) dated 12 August 2010 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

The following rejections of record in the previous Office Action are maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Section [0001]**

Claims 35-38, 41-44, 48, 49 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of EP 0605963 A2 to Wright (of record), as evidenced by "WHO Food Additives Series No. 5" (of record).

Sommermeyer *et al.* teach compounds comprising a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxylalkyl starch is coupled to the

active ingredient either directly or via a linker (paragraph 0029). HAS is preferably oxidized at the reducing end prior to binding to the active ingredient (paragraph 0031). Hydroxyethyl starch (HES) is the preferred HAS (paragraph 0050). HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch in a concentration of up to 95% (paragraph 0019). Any physiologically compatible HES can be used as the starting material, although HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134). HES preferably has a molar degree of substitution of 0.1 to 0.8 and a ratio of $C_2$:$C_6$ substitution in the range of 2 to 20 (paragraph 0134). When HAS is bound to the active ingredient via a linker, the linker may be an amino acid, hydrazine or oxylamine derivative, among others (paragraph 0126).

It is noted that Sommermeyer *et al.* do not expressly indicate that HES used in the conjugation is amylopectin degradation fractions. However, as evidenced by the article entitled "WHO Food Additives Series No. 5" (of record), the molecular weight of waxy corn starch can be as high as 80,000,000. Therefore, since Sommermeyer *et al.* disclose that HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch (paragraph 0019) and preferably uses HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134), it is the Office's position that the HES described by Sommermeyer *et al.* is derived from amylopectin degradation fractions to obtain HES with an average molecular weight of 2 to 40 kD.

The teachings of Sommermeyer *et al.* differ from that of the instantly claimed invention in that Sommermeyer *et al.* do not disclose conjugation of oxidized HES to a

linker wherein the end of the linker directly conjugated to HES forms an ester bond with oxidized HES upon conjugation.

Wright discloses water-soluble polymers that are modified to form a hydrazone linkage with an aldehyde group on a protein. Glycoproteins, i.e., polypeptides covalently joined to a carbohydrate molecule or molecules, provide additional opportunities for providing different methods of water-soluble polymer derivatization of a polypeptide because of the presence of the carbohydrate moieties on the polypeptide. Water-soluble polymer reagents may be coupled directly to the carbohydrate moieties of glycoproteins as opposed to the amino acid polypeptide backbone, i.e., various functional groups present on the polypeptide, of the glycoprotein. It may be advantageous to couple water-soluble reagents to the carbohydrate moieties of the glycoprotein rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hindrance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified protein (p. 3, lines 38-46). Examples of water-soluble polymers (P) include, *inter alia*, dextran and dextran derivatives, cellulose and cellulose derivatives, starch and their derivatives, polyalkylene glycol and derivatives thereof, heparin and fragments of heparin (p. 7, line 54 – p. 8, line 16). Modified water-soluble polymers that are useful for conjugation to polypeptides include water-soluble polymers modified with a hydrazine or oxylamine group on the end of the linker to be conjugated to the polypeptide. The polypeptide is conjugated to the water-soluble polymer via an oxygen, as in, for example, formula (I) and formulas (XIX) –

(XXVII), or a nitrogen linkage, as in, for example, formula (III) – (VIII) (p. 7, lines 19-53). The water-soluble polymer reagents may be covalently attached to proteins through reactions with aldehyde groups introduced onto the carbohydrate moieties of the glycoprotein (p. 7, lines 5-18). The synthesis of hydrazine and oxylamine derivatives of water-soluble polymers are further exemplified wherein the water-soluble polymer is PEG (p. 12-18).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker, with the teachings of Wright, regarding the conjugation of water-soluble polymers to polypeptides via a hydrazone linkage. As Sommermeyer *et al.* teach that when oxidized HAS is bound to the active ingredient via a linker, the linker may be, *inter alia*, an amino acid, hydrazine or oxylamine derivative, and Wright teaches hydrazine and oxylamine linkers for use in conjugation of water-soluble polymers to polypeptides, it would have been *prima facie* obvious for one of ordinary skill in the art to use the disclosed hydrazine and oxylamine linkers disclosed by Wright for conjugation of the peptide to oxidized HAS, with the expectation that it would yield a predictable result. It is noted that although Sommermeyer *et al.* teach that amino acids, hydrazides and oxylamines may be used as linkers for conjugation of oxidized HAS to an active ingredient, Sommermeyer *et al.* do not expressly indicate whether the hydrazide or oxylamine functional groups are directly conjugated to HAS or to the active ingredient. However, as Wright teaches that

the hydrazide or oxylamine derivative can be conjugated to aldehyde groups introduced onto the carbohydrate moieties of the glycoprotein (active ingredient) rather than to the polypeptide backbone amino acids because of differences in charge displacement, steric hindrance, amino acid residues at active sites, and other problems that may disrupt the structure and function of the polypeptide component of the water-soluble polymer modified protein, one of ordinary skill in the art would have been motivated to combine the teachings of Sommermeyer *et al.* with Wright, and prepare hydrazine and oxylamine derivatives as disclosed in Formulas (I) and (XIX)-(XXVII), wherein P represents oxidized HAS, with the expectation that the resultant HAS-hydrazine derivative or HAS-oxylamine derivative could be used for conjugation to an active ingredient. Although not expressly taught, the combined teachings of Sommermeyer *et al.* and Wright suggest that the hydrazide and oxylamine derivatives of water-soluble polymers were purified in solution and concentrated to a solid form, thereby necessarily meeting the limitations of instant claims 48 and 49.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

*Response to Arguments*

Applicant's arguments, filed 12 August 2010 and the Declaration of Dr. Klaus Sommermeyer, submitted on 12 August 2010 under 37 CFR § 1.132, with respect to the rejection of claims 35-38, 41-44, 48, 49 and 69 made under 35 USC § 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view

of EP 0605963 A2 to Wright, as evidenced by "WHO Food Additives Series No. 5," have been fully considered but they are not persuasive.

Applicant argues that contrary to the Examiner's allegations, example 2 of Sommermeyer does not disclose an isolated ester of an aldonic acid, and therefore, does not render the instantly claimed invention obvious in view of the combined teachings of the prior art. Applicant further provides a Declaration under 37 CFR § 1.132, stating that the reaction of HES, oxidized at the reducing end, with EDC and HOBt according to example 2 of the Sommermeyer reference was performed in an aqueous solution, and therefore does not produce an "isolated ester," as claim in claim 35, but rather, forms a very reactive O-acylisourea intermediate. The Declaration further states that such stable esters as claimed in claim 35 are only obtainable in anhydrous solvents. Applicant's arguments and the Declaration of Dr. Sommermeyer have been carefully considered but are not persuasive. It appears from Applicant's arguments that Applicant has misunderstood the rejection of the claims over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view of EP 0605963 A2 to Wright, as evidenced by "WHO Food Additives Series No. 5." The applied rejection does not involve the reaction and intermediates of example 2 of Sommermeyer *et al.* Rather, the rejection involves the teachings of the use of a linker for conjugating HES to an active ingredient in Sommermeyer *et al.* Although Sommermeyer *et al.* suggest that the active ingredient may be conjugated to HES via a linker, Sommermeyer *et al.* do not teach any specific linker, other than to teach that the linker may be an amino acid, hydrazine or oxylamine derivative, among others. Therefore, the teachings of Wright

were included to overcome this deficiency in the teachings of Sommermeyer *et al.* Specifically, Wright teaches the conjugation of glycoproteins to water-soluble polymers that have been modified to form a hydrazone linkage with an aldehyde group on the protein. Examples of hydrazine modified water-soluble polymers are disclosed as formulas (I)-(IX) and examples of hydroxylamine modified water-soluble polymers are disclosed as formulas (XIX)-(XXVII). Wright further teaches that examples of water-soluble polymers include, *inter alia*, dextran and dextran derivatives, cellulose and cellulose derivatives, starch and their derivatives, polyalkylene glycol and derivatives thereof. Therefore, as discussed in the rejection of record shown above, it would have been *prima facie* obvious for one of ordinary skill in the art to use any of the linkers disclosed in Wright for conjugation of HES with an active ingredient, as taught in Sommermeyer *et al.* One of ordinary skill in the art would have been motivated to use the linkers disclosed by Wright in order to receive the expected benefit, as disclosed by Wright, that conjugation of water-soluble reagents to the carbohydrate moieties of the glycoprotein rather than to the polypeptide backbone amino acids may overcome issues of steric hindrance and disruption of active sites if conjugated to the amino acid residues. Furthermore, as Sommermeyer *et al.* teach that hydrazine and oxylamine linkers may be used for conjugation of HES to an active ingredient, and the linkers taught by Wright are functionalized with a hydrazine or oxylamine group for conjugation to the glycoprotein, one of ordinary skill in the art would have a reasonable expectation of success in using the linkers disclosed by Wright. Although not expressly taught, it would be immediately obvious to one of ordinary skill in the art that using a linker such

as that in formula (I) or formula (XIX) of Wright, wherein P represents HES, and conjugation occurs at the reducing end of HES that is oxidized, as disclosed by Sommermeyer *et al.*, results in an isolated aldonic acid ester.

Therefore, Applicant's arguments and the Declaration of Dr. Klaus Sommermeyer are ineffective to rebut the *prima facie* case herein.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art, as discussed above.

The rejection is still deemed proper and therefore maintained.

**Section [0002]**

Claims 35-38, 41-49 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record).

Sommermeyer *et al.* teach compounds comprising a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxylalkyl starch is coupled to the active ingredient either directly or via a linker (paragraph 0029). HAS is preferably oxidized at the reducing end prior to binding to the active ingredient (paragraph 0031). Hydroxyethyl starch (HES) is the preferred HAS (paragraph 0050). HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch in a

concentration of up to 95% (paragraph 0019). Any physiologically compatible HES can be used as the starting material, although HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134). HES preferably has a molar degree of substitution of 0.1 to 0.8 and a ratio of $C_2$:$C_6$ substitution in the range of 2 to 20 (paragraph 0134). When HAS is bound to the active ingredient via a linker, the linker may be an amino acid, hydrazine or oxylamine derivative, among others (paragraph 0126).

Sommermeyer *et al.* disclose in Example 2 (paragraph 0147) a compound wherein hydroxyethyl starch oxidized at the reducing end is reacted with HSA in the presence of EDC, in water. This is further exemplified in Table 2 (p. 11). Although not expressly indicated by Sommermeyer *et al.*, it is evidenced by Marder *et al.* that when an acid (i.e. oxidized hydroxyethyl starch) is reacted with EDC, an O-acylisourea intermediate, containing an ester linkage (compound (1) of Figure 1), is formed. When this reaction takes place in the presence of HOBt, an ester (as defined by Applicant on p. 9 of the Specification) is formed, that between the acid and the hydroxyl group of HOBt (see compound (5) in Figure 1).

It is noted that Sommermeyer *et al.* do not expressly indicate that HES used in the conjugation is amylopectin degradation fractions. However, as evidenced by the article entitled "WHO Food Additives Series No. 5" (of record), the molecular weight of waxy corn starch can be as high as 80,000,000. Therefore, since Sommermeyer *et al.* disclose that HES is a substituted derivative of the carbohydrate polymer amylopectin which occurs in maize starch (paragraph 0019) and preferably uses HES with an average molecular weight of 2 to 40 kD is preferred (paragraph 0134), it is the Office's

position that the HES described by Sommermeyer *et al.* is derived from amylopectin degradation fractions to obtain HES with an average molecular weight of 2 to 40 kD.

Although Sommermeyer *et al.* teach the activation of HES with EDC/HOBt prior to conjugation with HSA, Sommermeyer *et al.* do not teach that this activated ester intermediate is, or can be, isolated.

Hermanson teaches that EDC, a popular carbodiimide used in conjugation of biological substances, is labile in the presence of water (p. 170, section 1.1, paragraph 1). In the aqueous solutions, the oxygen atom of water can act as a nucloephile. Thus, hydrolysis of the O-acylisourea intermediate is a major competing reaction (p. 170, section 1.1, paragraph 2). An alternative is to use EDC in the presence of sulfo-N-hydroxysuccinimide (sulfo-NHS). Forming a sulfo-NHS ester intermediate from the reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activated carboxylate group to hours (p. 173, section 1.2, paragraph 2). Furthermore, EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, section 1.3, paragraph 3). A protein can be incubated in the presence of EDC/sulfo-NHS and the active ester form can be isolated. The isolated active ester is then mixed with a second protein or other amine-containing molecule for conjugation (p. 173, last paragraph). This two step process allows the active species to form only on one protein, thus gaining greater control over the conjugation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of

hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC. One of ordinary skill in the art would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Hermanson, that the reaction of the hydroxyl group on sulfo-NHS with the EDC active-ester complex extends the half-life of the activate carboxylate group to hours (p. 173, section 1.2, paragraph 2) and that this reaction usually increases the yield of conjugation dramatically over that obtainable solely with EDC (p. 173, section 1.3, paragraph 3). Furthermore, one of ordinary skill in the art would have been motivated to combine the teachings and modify the conjugation procedure taught by Sommermeyer *et al.* such that the activated ester intermediate of HES is isolated prior to conjugation with HSA, in order to receive the expected benefit, as suggested by Hermanson, that sulfo-NHS activated ester complexes can be isolated before conjugation to another compound, thereby permitting greater control over the conjugation as only one reaction can occur to form the desired product rather than the formation of side products which can occur when intermediates are not isolated from their reaction conditions.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

*Response to Arguments*

Applicant's arguments, filed 12 August 2010 and the Declaration of Dr. Klaus Sommermeyer, submitted on 12 August 2010 under 37 CFR § 1.132, with respect to the rejection of claims 35-38, 41-49 and 69 made under 35 USC § 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view of in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson, as evidenced by Marder *et al.*, and as evidenced by "WHO Food Additives Series No. 5," have been fully considered but they are not persuasive.

Applicant argues that contrary to the Examiner's allegations, example 2 of Sommermeyer does not disclose an isolated ester of an aldonic acid, and therefore, does not render the instantly claimed invention obvious in view of the combined teachings of the prior art. Applicant further provides a Declaration under 37 CFR § 1.132, stating that the reaction of HES, oxidized at the reducing end, with EDC and HOBt according to example 2 of the Sommermeyer reference was performed in an aqueous solution, and therefore does not produce an "isolated ester," as claim in claim 35, but rather, forms a very reactive O-acylisourea intermediate. The Declaration further states that such stable esters as claimed in claim 35 are only obtainable in anhydrous solvents. Applicant's arguments and the Declaration of Dr. Sommermeyer have been carefully considered but are not persuasive.

Applicant's arguments and the Declaration of Dr. Sommermeyer are directed only towards the teachings of Sommermeyer *et al.* However, Applicant is requested to note that the instant rejection is made over the combined teachings of the prior art. One

cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is noted that Applicant further argues that the secondary references do not remedy the deficiencies of Sommermeyer *et al.* However, the Examiner disagrees. As Dr. Sommermeyer stated in his Declaration, stable esters with EDC are difficult to obtain in aqueous solutions, much less in isolable form. The teachings of the secondary reference by Hermanson agree with Dr. Sommermeyer's statement, teaching that EDC active intermediates are labile in the presence of water. Thus, Hermanson teaches that an alternative to using EDC is to use sulfo-NHS, which will extend the half-life of the activated carboxylate group to hours. Furthermore, Hermanson teaches that EDC/sulfo-NHS-coupled reactions are highly efficient and usually increase the yield of conjugation dramatically over that obtainable solely with EDC. Moreover, the active ester form can be isolated. In view of the teachings of Hermanson, one of ordinary skill in the art would have been motivated to substitute the EDC/HOBt coupling reaction of example 2, as disclosed by Sommermeyer *et al.*, with the EDC/sulfo-NHS reagents as disclosed by Hermanson. Furthermore, one of ordinary skill in the art would have been motivated to isolate the NHS-activated ester as Hermanson teaches that this two step process allows the active species to form only one protein, thereby gaining greater control over the conjugation reaction. Additionally, while Applicant argues that the reaction in EDC results in a very reactive O-acylisourea intermediate, and not an ester, Applicant is requested to note that example 2 of Sommermeyer *et al.* also teaches the

use of HOBt in the EDC coupling reaction, which would result in an ester intermediate, as evidenced by Marder *et al.*

Therefore, Applicant's arguments and the Declaration of Dr. Klaus Sommermeyer are ineffective to rebut the *prima facie* case herein.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art, as discussed above.

The rejection is still deemed proper and therefore maintained.

**Section [0003]**

Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record), as applied to claims 35-38, 41-49 and 69, further in view of journal publication to Gunja *et al.* (of record), in view of journal publication by Mua *et al.* (of record).

The teachings of Sommermeyer *et al.*, Hermanson, Marder *et al.* and the publication by WHO were as disclosed in section [0002] above of the claim rejections under 35 USC § 103.

Sommermeyer *et al.* is silent with regards to the average branching of $\alpha$-1,6-glycosidic linkages in the starch fractions.

Gunja *et al.* teach the enzymic conversion of amylopectin into glycogen-type polysaccharide. Table 2 shows that potato amylopectin has an average of 4-5% of α-1,6-glycosidic linkages (p. 1017, column 2). The introduction of the yeast branching enzyme further increases the branching by approximately 2-9% (p. 1017, column 2, last paragraph), resulting in a degree of branching of up to 14%.

Mua *et al.* teach the gel textural attributes of corn starch amylose and amylopectin fractions that vary in molecular weight and degree of branching. Starches isolated from different botanical sources have different functional properties and are used in foods and non-food products (p. 157, column 1). For amylopectin, the molecular structure and degree of branching govern the starches' gel textural properties (abstract). Highly branched amylopectins exhibit decreased ahdesive force and increased stringiness (p. 164, column 2). Knowing the relationships between the molecular structure and functional attributes of the starch could pave the way for new and improved starch uses (p. 157, column 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC, with the teachings of Gunja, regarding the use of a yeast enzyme to increase the degree of branching in amylopectin from 4-5% up to 14%, with the teachings of Mua *et al.*, regarding the influence branching has on the gelling

properties of amylopectin. One of ordinary skill in the art would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Mua *et al.*, that the degree of branching can be used to affect the gelling properties of amylopectin. Thus, it is considered *prima facie* obvious for one of ordinary skill in the art to choose an amylopectin, with the appropriate degree of branching to yield a product with the desired gelling properties, for conjugation to a drug.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

*Response to Arguments*

Applicant's arguments, filed 12 August 2010 and the Declaration of Dr. Klaus Sommermeyer, submitted on 12 August 2010 under 37 CFR § 1.132, with respect to the rejection of claims 39 and 40 made under 35 USC § 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view of in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson, as evidenced by Marder *et al.*, and as evidenced by "WHO Food Additives Series No. 5," as applied to claims 35-38, 41-49 and 69, further in view of journal publication to Gunja *et al.*, in view of journal publication by Mua *et al.*, have been fully considered but they are not persuasive.

Applicant argues that claims 39 and 40 depend directly or indirectly from claim 35, which Applicant argued as being non-obvious over Sommermeyer *et al.*, as indicated in the "Response to Arguments" heading under section [0002] above. Additionally, Applicant argues that the secondary references do not remedy the

deficiencies of Sommermeyer *et al.*, and therefore, claims 39 and 40 are also non-obvious over Sommermeyer *et al.* Applicant's arguments have been fully considered but are not persuasive. As discussed in the "Response to Arguments" heading under section [0002] above, the combined teachings of Sommermeyer *et al.* and Hermanson render instant claim 35 obvious. Therefore, the inclusion of the teachings of Gunja *et al.* and Mua *et al.* is sufficient to show why one of ordinary skill in the art would have been motivated to use a starch fraction with an average branching of 5-10 mol%, or 10-25 mol%, of $\alpha$1,6-glycosidic linkages. The claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art, as discussed above.

The rejection is still deemed proper and therefore maintained.

**Section [0004]**

Claims 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.* (IDS dated 26 June 2008, PG Pub No. US 2005/0063943 A1 used as English equivalent translation), in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson (of record), as evidenced by Marder *et al.* (of record), and as evidenced by "WHO Food Additives Series No. 5" (of record), as applied to claims 35-38, 41-49 and 69, further in view of journal publication to Nozaki *et al.* (of record).

The teachings of Sommermeyer *et al.*, Hermanson, Marder *et al.* and the publication by WHO were as disclosed in section [0002] above of the claim rejections under 35 USC § 103.

The conjugation reaction mediated by EDC/HOBt, disclosed by Sommermeyer *et al.*, occurs in water. However, Hermanson teaches that an EDC conjugate is labile in the presence of water and thus can undergo hydrolysis. Thus, it would have been *prima facie* obvious to one of ordinary skill in the art, a chemist, that it would be preferable have the aldonic acid ester in an aprotic organic solvent, such as DMF or DMSO, rather than in water, so as to avoid hydrolysis of the aldonic acid ester. Although discussed with a different carbodiimide, this point is further illustrated by Hermanson in saying that "active ester synthesis done…in an organic solvent…does not have the hydrolysis problems of water-soluble EDC-formed ester" (p. 178).

Nozaki *et al.* disclose peptide coupling reactions mediated by EDC and an additive in both aqueous media and in aprotic organic media. A comparison of three additives, HOBt, HOSu (NHS), and HONb, and four different solvent conditions, DMF, 4:1 DMF/water, 1:4 DMF/water, and water were studied and the results of their coupling yield are disclosed in Table 1 (p. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Sommermeyer *et al.*, concerning a conjugate of hydroxyalkyl starch (HAS) and an active ingredient, wherein the hydroxyalkyl starch is coupled to the active ingredient either directly or via a linker using EDC, with the teachings of Hermanson, regarding the use of EDC/sulfo-NHS in a conjugation reaction as an alternative to EDC, with the teachings of Nozaki, regarding the use of additives, such as HOBt, HOSu and HONb in peptide coupling reactions mediated by EDC. Although Nozaki teach that peptide coupling reactions mediated by EDC and an

additive can occur in an aqueous medium, in view of the teachings of Hermanson that an EDC conjugate is labile in the presence of water and thus can undergo hydrolysis, one of ordinary skill in the art would have been motivated to minimize the amount of water in the solvent, preferably using an aprotic organic solvent for the reaction, such as DMF as disclosed by Nozaki, with the expectation that the use of this solvent would minimize any potential hydrolysis reactions, and increase the reaction yield.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

*Response to Arguments*

Applicant's arguments, filed 12 August 2010 and the Declaration of Dr. Klaus Sommermeyer, submitted on 12 August 2010 under 37 CFR § 1.132, with respect to the rejection of claims 50-53 made under 35 USC § 103(a) as being unpatentable over WIPO publication WO 2002/080979 by Sommermeyer *et al.*, in view of in view of chapter entitled "Zero-Length Cross-linkers" by Hermanson, as evidenced by Marder *et al.*, and as evidenced by "WHO Food Additives Series No. 5," as applied to claims 35-38, 41-49 and 69, further in view of journal publication to Nozaki *et al.*, have been fully considered but they are not persuasive.

Applicant argues that claims 50-53 depend directly or indirectly from claim 35, which Applicant argued as being non-obvious over Sommermeyer *et al.*, as indicated in the "Response to Arguments" heading under section [0002] above. Additionally, Applicant argues that the secondary references do not remedy the deficiencies of

Sommermeyer *et al.*, and therefore, claims 50-53 are also non-obvious over Sommermeyer *et al.* Applicant's arguments have been fully considered but are not persuasive. As discussed in the "Response to Arguments" heading under section [0002] above, the combined teachings of Sommermeyer *et al.* and Hermanson render instant claim 35 obvious. Therefore, the additional teachings of Hermanson and the inclusion of the teachings of Nozaki *et al.* is sufficient to show why one of ordinary skill in the art would have been motivated to use an aprotic organic solvent in their conjugation reaction. The claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art, as discussed above.

The rejection is still deemed proper and therefore maintained.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35-38, 42-53 and 69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 61-79 of copending U.S. application no. 10/542,944.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to an aprotic-solvent soluble carbonic diester of HES, having a mean molecular weight in the range of 2000-300000 Da, a degree of substitution between 0.1 and 0.8, and a C2/C6 ratio of the substituents on the carbon atoms C2 and C6 of the anhydroglucoses between 2 and 15, and having a mean content of from 1:1 to 10:1 of carbonic diester substitutents per HES molecule. The alcohol component from which the carbonic diester is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 64-66). The copending application is also drawn to a solid or solution comprising at least one of the disclosed carbonic diesters (claims 67 and 68). The solution comprises DMSO, DMF, DMS or N-methylpyrrolidone (claim 69). The copending application is also drawn to a method for production of HES carboxylic diesters, and a method of producing pharmaceutically active substances comprising reacting at least one HES carbonic diester with a pharmaceutical active substance.

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. They hydroxyalkyl starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol

group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS or N-methylpyrrolidone (claims 51-53).

Thus, the instant claims 35-38, 42-53 and 69 are seen to be anticipated by claims 61-79 of copending U.S. application no. 10/542,944.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 35-38 and 42-49 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 15 and 16 of copending U.S. application no. 10/590,676.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for the production of hyperbranched amylopectin. The method further includes a step of oxidizing the terminal reducing end of the hydrolysis product to the aldonic acid, and activating the aldonic acid group to the aldonic acid ester group. The Specification discloses that the aldonic acid ester group is derived from N,N'-disuccinimidyl carbonate.

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. They hydroxyalkyl

starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS and N-methylpyrrolidone (claims 51-53).

The claims of the copending application do not expressly disclose isolation of the aldonic acid ester or solid or solution comprising the aldonic acid ester. However, it would have been *prima facie* obvious to one of ordinary skill in the art to purify the aldonic acid ester prior to further reacting it with a pharmaceutical ingredient in order to minimize potential side reactions that may occur due to the use of impure reactants.

Thus, the instant claims 35-38 and 42-49 are seen to be obvious over claims 15 and 16 of copending U.S. application no. 10/590,676.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 35-38, 41-53 and 69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-22 of copending U.S. application no. 11/518,558.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to a method for preparing a conjugate comprising a protein and a HAS polymer derivative. The HES has a molecular weight of from 2 to 200 kD. The method comprises selectively oxidizing the polymer at its reducing end and reacting the oxidized polymer with N,N'-disuccinimidyl carbonate at its oxidized reducing end to give a polymer derivative comprising a reactive carboxy group. The reactions are carried out in an anhydrous aprotic polar solvent, such as dimethyl acetamide of DMF (claim 22).

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. They hydroxyalkyl starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid

ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS and N-methylpyrrolidone (claims 51-53).

The claims of the copending application do not expressly disclose isolation of the aldonic acid ester or solid or solution comprising the aldonic acid ester. However, it would have been *prima facie* obvious to one of ordinary skill in the art to purify the aldonic acid ester prior to further reacting with protein to minimize potential side reactions that may occur due to impure reactants.

Thus, the instant claims 35-38, 41-53 and 69 are seen to be obvious over claims 16-22 of copending U.S. application no. 11/518,558.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 35-38, 41, 42 and 48-53 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of U.S. Patent No. 7,115,576 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent is drawn to a water-soluble antibiotic derivative represented by structural formula (I), wherein B may be HES, or soluble amylopectin in HES form. The mean molecular weight of the HES is in the range between 2000 and 200000 Da (claim 4). The HES displays a degree of substitution in the range of 0.3 to 0.5 (claim 8). The HES displays a C2/C6 substitution ratio in the range of 2 to 12 (claim 9). The claims of the patent are also drawn to a method of preparing the water-soluble

antibiotic derivative represented by structural formula (II). The polysaccharide is oxidized at the reducing end (claim 17).

The claims of the instant application are drawn to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch. They hydroxyalkyl starch is HES or hydroxypropyl starch (claims 41 and 69). The average molecular weight of the HES is in the range of 2-300000 Da, and the level of molar substitution is between 0.1 and 0.8, and the C2/C6 ratio of substituents on carbon atoms C2 and C6 of the anhydroglucoses is between 2 and 15 (claim 43). The alcohol component of the aldonic acid ester from which it is derived from comprises an HO-N group or a phenol group, preferably selected from N-hydroxysuccinimide, sulfo-N-hydroxysuccinimide, substituted phenols, and hydroxybenzotriazole (claims 45-47). The instant application is also drawn to a solid or solution comprising at least one polysaccharide aldonic acid ester (claims 48 and 49). The solution comprises DMSO, DMF, DMS and N-methylpyrrolidone (claims 51-53).

Thus, the instant claims 35-38, 41, 42 and 48-53 are seen to be anticipated by claims 1-32 of U.S. Patent No. 7,115,576 B2.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

*Response to Arguments*

Applicant's request that the provisional obviousness-type double-patenting rejections be withdrawn provided that the claims of the instant application are otherwise

in condition for allowance before those of copending application nos. 10/542,944, 10/590,676 and 11/518,558, in the reply filed on 12 August 2010, is acknowledged.

However, as the claims of the instant application have not yet been found to be allowable, the rejections are still deemed proper and therefore maintained.

With regards to the obviousness-type double-patenting rejection over U.S. Patent No. 7,115,576 B2, Applicant argues that the instant claims are directed to an isolated aldonic acid ester of a polysaccharide, starch or hydroxylalkyl derivatized starch whereas the claims of the '576 patent is directed to a water-soluble antibiotic derivative. Applicant further argues that the '576 patent teaches coupling of pharmaceutical active ingredients in anhydrous aprotic solvents, such as DMSO, whereas the instant application allows coupling reactions in aqueous media. Thus, in view of the cited differences, Applicant requests that the obviousness-type double-patenting rejection over U.S. Patent No. 7,115,576 B2 be withdrawn. Applicant's arguments have been carefully considered but are not persuasive. Although Applicant argues that the '576 patent is drawn to a water-soluble antibiotic derivative whereas the instant application is drawn to an isolated aldonic acid ester of a polysaccharide, the compound of formula (II) in the '576 patent falls within the definition of aldonic acid ester when B is an HES polysaccharide oxidized at the reducing end, and therefore, is encompassed within the claim limitations. Furthermore, although Applicant argues the instant application allows coupling reactions in aqueous media whereas the '576 patent teaches coupling of a pharmaceutical active ingredient in anhydrous aprotic solvent, Applicant is requested to

note that instant claims 35-38, 41, 42 and 48 do not contain any solvent limitation and claims 49, 50, 52 and 53 do not require any presence of water as a solvent. Furthermore, the '576 patent expressly states that the compound of formula (II) is water-soluble and the claims, for example, claim 18, does not require that the organic solvent, DMSO, be anhydrous. The rejection is still deemed proper and therefore maintained.

***Conclusion***

In view of the rejections to the pending claims set forth above, no claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-

270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
Art Unit 1623